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=> d his

     (FILE 'HOME' ENTERED AT 14:59:00 ON 20 MAY 2003)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 15:00:34 ON 20 MAY 2003
L1        115622 S CALMODULIN
L2         64490 S CALCIUM AND L1
L3         28975 S L2 (A) KINASE?
L4        232176 S CELL (A) DEATH
L5           109 S "DRP-1"
L6           478 S L3 AND L4
L7             9 S L5 AND L6
L8             5 DUP REM L7 (4 DUPLICATES REMOVED)
L9        387738 S APOPTOSIS
L10          578 S L3 AND L9
L11            9 S L5 AND L10
L12            6 DUP REM L11 (3 DUPLICATES REMOVED)
L13           55 S L5 AND HUMAN
L14           23 DUP REM L13 (32 DUPLICATES REMOVED)
L15       499589 S L4 OR L9
L16            5 S L14 AND L15
L17            5 DUP REM L16 (0 DUPLICATES REMOVED)
                 E KIMCHI A/AU
L18          499 S E3
L19           10 S L5 AND L18
L20            4 DUP REM L19 (6 DUPLICATES REMOVED)
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NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
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NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
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NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
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NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Apr 21	Indexing from 1947 to 1956 being added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and

right truncation

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
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=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
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=> s calmodulin
L1 115622 CALMODULIN

=> s calcium and l1
L2 64490 CALCIUM AND L1

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=> s l2 (a) kinase?
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L10 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L11 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L12 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L13 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L14 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L15 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L16 (A) KINASE?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L17 (A) KINASE?'
L3       28975 L2 (A) KINASE?

=> s cell (a) death
   3 FILES SEARCHED...
L4      232176 CELL (A) DEATH

=> s "DRP-1"
L5         109 "DRP-1"

=> s l3 and l4
L6         478 L3 AND L4

=> s l5 and l6
L7           9 L5 AND L6

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8           5 DUP REM L7 (4 DUPLICATES REMOVED)

=> d 1-5 ibib ab

L8   ANSWER 1 OF 5  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER:   2002278596  EMBASE
TITLE:              DAP kinase and DRP-1 mediate
                    membrane blebbing and the formation of autophagic vesicles
                    during programmed cell death.
AUTHOR:             Inbal B.; Bialik S.; Sabanay I.; Shani G.; Kimchi A.
CORPORATE SOURCE:   A. Kimchi, Dept. of Molecular Genetics, Weizmann Institute
                    of Science, Rehovot 76100, Israel.
                    Adi.kimchi@weizmann.ac.il
SOURCE:             Journal of Cell Biology, (29 Apr 2002) 157/3 (455-468).
                    Refs: 48
                    ISSN: 0021-9525  CODEN: JCLBA3
COUNTRY:            United States
DOCUMENT TYPE:      Journal; Article
FILE SEGMENT:       029     Clinical Biochemistry
LANGUAGE:           English
SUMMARY LANGUAGE:   English
AB   Death-associated protein kinase (DAPk) and DAPk-related protein
     kinase (DRP)-1 proteins are Ca(+2)/
     calmodulin-regulated Ser/Thr death kinases whose precise
     roles in programmed cell death are still mostly
     unknown. In this study, we dissected the subcellular events in which these
     kinases are involved during cell death.
```

Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of **cell death**, and extensive autophagy, which is typical of autophagic (type II) programmed **cell death**. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or **DRP-1** reduced membrane blebbing during the p55/tumor necrosis factor receptor 1-induced type I apoptosis but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of **DRP-1** or of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-.gamma.. Thus, both endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this **kinase** in the process of autophagy.

L8 ANSWER 2 OF 5 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002687075 MEDLINE
DOCUMENT NUMBER: 22334988 PubMed ID: 12445458
TITLE: The DAP-**kinase** family of proteins: study of a novel group of **calcium**-regulated death-promoting **kinases**.
AUTHOR: Shohat Galit; Shani Gidi; Eisenstein Miriam; Kimchi Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, 76100, Rehovot, Israel.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (2002 Nov 4) 1600 (1-2) 45-50. Ref: 15
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030102
Entered Medline: 20021231

AB DAP-**kinase** (DAPk) is a Ca(2+)/**calmodulin** (CaM)-regulated Ser/Thr **kinase** that functions as a positive mediator of programmed **cell death**. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional **kinases** have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca(2+)/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation on a conserved serine at position 308, in the CaM regulatory domains of these two **kinases**. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these **kinases**, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two **kinases** to their common activator-CaM. In DAPk, the dephosphorylation of serine 308 also increases the Ca(2+)/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity.

These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting **kinases** silent in healthy cells and ensures their activation only in response to apoptotic signals.

L8 ANSWER 3 OF 5 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2002:977272 SCISEARCH
THE GENUINE ARTICLE: 620DD
TITLE: The DAP-**kinase** family of proteins: study of a novel group of **calcium**-regulated death-promoting **kinases**.
AUTHOR: Shohat G; Shani G; Eisenstein M; Kimchi A (Reprint)
CORPORATE SOURCE: Weizmann Inst Sci, Dept Mol Genet, IL-76100 Rehovot, Israel (Reprint); Weizmann Inst Sci, Dept Chem Serv, IL-76100 Rehovot, Israel
COUNTRY OF AUTHOR: Israel
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEINS AND PROTEOMICS, (4 NOV 2002) Vol. 1600, No. 1-2, pp. 45-50.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 1570-9639.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 15

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB DAP-**kinase** (DAPk) is a Ca2+/**calmodulin** (CaM)-regulated Ser/Thr **kinase** that functions as a positive mediator of programmed **cell death**. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional **kinases** have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca2+/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation on a conserved serine at position 308, in the CaM regulatory domains of these two **kinases**. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these **kinases**, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two **kinases** to their common activator-CaM. In DAR, the dephosphorylation of serine 308 also increases the Ca2+/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity. These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting **kinases** silent in healthy cells and ensures their activation only in response to apoptotic signals.

L8 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2000:95729 BIOSIS

DOCUMENT NUMBER: PREV200000095729
TITLE: Death-associated protein **kinase**-related protein 1, a novel serine/threonine **kinase** involved in apoptosis.
AUTHOR(S): Inbal, Boaz; Shani, Gidi; Cohen, Ofer; Kissil, Joseph L.; Kimchi, Adi (1)
CORPORATE SOURCE: (1) Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, 76100 Israel
SOURCE: Molecular and Cellular Biology, (Feb., 2000) Vol. 20, No. 3, pp. 1044-1054.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca2+/**calmodulin** (CaM)-regulated serine threonine **kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP **kinase** **DRP-1**, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of serine/threonine **kinases**. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca2+/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active **kinase**. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP **kinase**. Possible functional connections between DAP **kinase** and **DRP-1** are discussed.

L8 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of **cell death**-promoting DAP-**kinase** related protein **kinase** **DRP-1** and
INVENTOR(S): Kimchi, Adi
PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9944408	A1	20000105	AU 1999-44408	19990615
GB 2354522	A1	20010328	GB 2001-660	19990615
PRIORITY APPLN. INFO.:			US 1998-89294P P	19980615
			WO 1999-US13411 W	19990615

AB A new protein **kinase**, DAP-**Kinase** related 1 protein (**DRP-1**), which is a novel homolog of DAP-**kinase** , has been isolated. and cDNA sequence and amino acid sequences of human **DRP-1** are reported. This novel **calmodulin** -dependent **kinase** is a **cell death**-promoting protein functioning in the biochem. pathway which involves DAP (death-assocd. protein)-**kinase** (e.g., forming a cascade of sequential **kinases**, one directly activating the other). Alternatively, the two **kinases** may operate to promote **cell death** in parallel pathways.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 15:00:34 ON 20 MAY 2003

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L1       115622 S CALMODULIN
L2        64490 S CALCIUM AND L1
L3        28975 S L2 (A) KINASE?
L4       232176 S CELL (A) DEATH
L5          109 S "DRP-1"
L6          478 S L3 AND L4
L7            9 S L5 AND L6
L8            5 DUP REM L7 (4 DUPLICATES REMOVED)

=> s apoptosis
L9       387738 APOPTOSIS

=> s l3 and l9
L10         578 L3 AND L9

=> s l5 and l10
L11           9 L5 AND L10

=> dup rem l11
PROCESSING COMPLETED FOR L11
L12           6 DUP REM L11 (3 DUPLICATES REMOVED)

=> d 1-6 ibib ab
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L12 ANSWER 1 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002278596 EMBASE
TITLE: DAP **kinase** and **DRP-1** mediate membrane blebbing and the formation of autophagic vesicles during programmed cell death.
AUTHOR: Inbal B.; Bialik S.; Sabanay I.; Shani G.; Kimchi A.
CORPORATE SOURCE: A. Kimchi, Dept. of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel. Adi.kimchi@weizmann.ac.il
SOURCE: Journal of Cell Biology, (29 Apr 2002) 157/3 (455-468). Refs: 48
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Death-associated protein **kinase** (DAPk) and DAPk-related protein **kinase** (**DRP**)-**1** proteins are Ca(+2)/**calmodulin**-regulated Ser/Thr death **kinases** whose precise roles in programmed cell death are still mostly unknown. In this study, we dissected the subcellular events in which these **kinases** are involved during cell death. Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of cell death, and extensive autophagy, which is typical of autophagic (type II) programmed cell death. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or **DRP-1** reduced membrane blebbing during the p55/tumor necrosis factor receptor 1-induced type I **apoptosis** but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of **DRP-1** or of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-.gamma.. Thus, both endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this **kinase** in the process of autophagy.

L12 ANSWER 2 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002687075 MEDLINE
DOCUMENT NUMBER: 22334988 PubMed ID: 12445458
TITLE: The DAP-**kinase** family of proteins: study of a novel group of **calcium**-regulated death-promoting **kinases**.
AUTHOR: Shohat Galit; Shani Gidi; Eisenstein Miriam; Kimchi Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, 76100, Rehovot, Israel.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (2002 Nov 4) 1600 (1-2) 45-50. Ref: 15
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021214
Last Updated on STN: 20030102
Entered Medline: 20021231

AB DAP-**kinase** (DAPk) is a Ca(2+)/**calmodulin** (CaM)-regulated Ser/Thr **kinase** that functions as a positive mediator of programmed cell death. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional **kinases** have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca(2+)/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation on a conserved serine at position 308, in the CaM regulatory domains of these two **kinases**. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these **kinases**, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two **kinases** to their common activator-CaM. In DAPk, the dephosphorylation of serine 308 also increases the Ca(2+)/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity. These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting **kinases** silent in healthy cells and ensures their activation only in response to apoptotic signals.

L12 ANSWER 3 OF 6 SCISEARCH COPYRIGHT 2003 THOMSON/ISI
ACCESSION NUMBER: 2002:977272 SCISEARCH
THE GENUINE ARTICLE: 620DD
TITLE: The DAP-**kinase** family of proteins: study of a novel group of **calcium**-regulated death-promoting **kinases**.
AUTHOR: Shohat G; Shani G; Eisenstein M; Kimchi A (Reprint)
CORPORATE SOURCE: Weizmann Inst Sci, Dept Mol Genet, IL-76100 Rehovot, Israel (Reprint); Weizmann Inst Sci, Dept Chem Serv, IL-76100 Rehovot, Israel
COUNTRY OF AUTHOR: Israel
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEINS AND PROTEOMICS, (4 NOV 2002) Vol. 1600, No. 1-2, pp. 45-50.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 1570-9639.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 15
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB DAP-**kinase** (DAPk) is a Ca2+/**calmodulin** (CaM)-regulated Ser/Thr **kinase** that functions as a positive mediator of programmed cell death. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional **kinases** have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca2+/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation

on a conserved serine at position 308, in the CaM regulatory domains of these two **kinases**. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these **kinases**, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two **kinases** to their common activator-CaM. In DAR, the dephosphorylation of serine 308 also increases the Ca2+/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity. These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting **kinases** silent in healthy cells and ensures their activation only in response to apoptotic signals. (C) 2002 Elsevier Science B.V. All rights reserved.

L12 ANSWER 4 OF 6 MEDLINE
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: 21153208 PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP-1 kinase** by controlling dimerization and **calmodulin** binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP-1** is a pro-apoptotic Ca2+/**calmodulin** (CaM)-regulated serine/threonine **kinase**, recently isolated as a novel member of the DAP-**kinase** family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP-1** homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP-1** dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP-1**, and a target for efficient activation of the **kinase** by various apoptotic stimuli.

L12 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
ACCESSION NUMBER: 2000:95729 BIOSIS

DOCUMENT NUMBER: PREV200000095729
TITLE: Death-associated protein **kinase**-related protein 1, a novel serine/threonine **kinase** involved in **apoptosis**.
AUTHOR(S): Inbal, Boaz; Shani, Gidi; Cohen, Ofer; Kissil, Joseph L.; Kimchi, Adi (1)
CORPORATE SOURCE: (1) Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, 76100 Israel
SOURCE: Molecular and Cellular Biology, (Feb., 2000) Vol. 20, No. 3, pp. 1044-1054.
ISSN: 0270-7306.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) **kinase**-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca2+/**calmodulin** (CaM)-regulated serine threonine **kinase** which shows high degree of homology to DAP **kinase**. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP **kinase** and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP **kinase** and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP **kinase** **DRP-1**, ZIP **kinase**, and DRAK1/2 together form a novel subfamily of serine/threonine **kinases**. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca2+/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active **kinase**. Ectopically expressed **DRP-1** induced **apoptosis** in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the **kinase**. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP **kinase** encompassing the death domain was found to block **apoptosis** induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP **kinase**. Possible functional connections between DAP **kinase** and **DRP-1** are discussed.

L12 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of cell death-promoting DAP-**kinase** related protein **kinase** **DRP-1** and
INVENTOR(S): Kimchi, Adi
PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9944408	A1	20000105	AU 1999-44408	19990615
GB 2354522	A1	20010328	GB 2001-660	19990615

PRIORITY APPLN. INFO.: US 1998-89294P P 19980615
WO 1999-US13411 W 19990615

AB A new protein **kinase**, DAP-**Kinase** related 1 protein (**DRP-1**), which is a novel homolog of DAP-**kinase** , has been isolated. and cDNA sequence and amino acid sequences of human **DRP-1** are reported. This novel **calmodulin** -dependent **kinase** is a cell death-promoting protein functioning in the biochem. pathway which involves DAP (death-assocd. protein)-**kinase** (e.g., forming a cascade of sequential **kinases**, one directly activating the other). Alternatively, the two **kinases** may operate to promote cell death in parallel pathways.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 14:59:00 ON 20 MAY 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 15:00:34 ON 20 MAY 2003

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L1        115622 S CALMODULIN
L2         64490 S CALCIUM AND L1
L3         28975 S L2 (A) KINASE?
L4        232176 S CELL (A) DEATH
L5           109 S "DRP-1"
L6           478 S L3 AND L4
L7             9 S L5 AND L6
L8             5 DUP REM L7 (4 DUPLICATES REMOVED)
L9        387738 S APOPTOSIS
L10          578 S L3 AND L9
L11            9 S L5 AND L10
L12            6 DUP REM L11 (3 DUPLICATES REMOVED)

=> s l5 and human
   4 FILES SEARCHED...
L13           55 L5 AND HUMAN

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           23 DUP REM L13 (32 DUPLICATES REMOVED)

=> d 1-23 ibib ab

L14   ANSWER 1 OF 23  BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-09951  BIOTECHDS
```

TITLE: **Human** dihydropyrimidinase-related protein 1 (**DRP-1**) 9.68 and encoded polynucleotide, used in diagnosis and treatment of malignant tumors, hemopathy, **human** immunodeficiency virus infection, immunological diseases and inflammation; plasmid and virus vector-mediated recombinant protein gene transfer and expression in host cell, DNA microarray, DNA chip, antisense and drug screening for cancer and HIV virus infection for diagnosis and genetherapy

AUTHOR: MAO Y; XIE Y
PATENT ASSIGNEE: SHANGHAI BIOWINDOW GENE DEV INC
PATENT INFO: WO 2002012314 14 Feb 2002
APPLICATION INFO: WO 2000-CN1045 26 Jun 2000
PRIORITY INFO: CN 2000-116757 26 Jun 2000
DOCUMENT TYPE: Patent
LANGUAGE: German
OTHER SOURCE: WPI: 2002-172142 [22]

AB DERWENT ABSTRACT:

NOVELTY - An isolated polypeptide (I) of **human** dihydropyrimidinase-related protein-1 (**DRP-1**) 9.68 containing an 88 residue amino acid sequence (S1), fully defined in the specification, or its fragment, analog or derivative, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated polynucleotide (II): (a) encoding (S1), or its fragment, analog or derivative; (b) complementary to (a); or (c) not less than 70 % homologous to (a) or (b); (2) a recombinant vector (III) containing an exogenous polynucleotide constructed from (II) and a plasmid, virus vector-expressing vector;(3) a genetically-modified host cell (IV) comprising (II) or (III); (4) producing (I) by culturing (IV) before isolating the product; (5) an antibody that specifically binds (I); (6) mimics or regulators of (I) activity or expression, preferably compounds that can mimic, promote, antagonize or inhibit **human** dihydropyrimidinase-related protein-1 (**DRP-1**) 9.68; (7) using the compounds of (6) for regulating (I) in vivo or in vitro; (8) detecting diseases relating to the novel polypeptide or disease susceptibility, by measuring the expression dose of (I), determining (I) activity, or detecting (I) expression dose caused by the polynucleotide that has abnormal activity due to a (II) mutation; (9) using (I) for screening mimics, agonists, antagonists or inhibitors, or for use in peptide fingerprinting identification; (10) using (II) as a primer for nucleic acid amplification reaction or as a probe for hybridization reaction, or in producing gene chips or microarrays; and (11) drug compositions for diseases relating to the (I) containing (I), (II), or mimics, agonists, antagonists, or inhibitors and their preparation in safe amounts with pharmaceutically-acceptable carrier, which can be used as diagnostics as well.

BIOTECHNOLOGY - Preferred Polypeptide: (I) is particularly one with not less than 95 % homology to (S1), especially one with an amino-acid sequence of (S1). Preferred Polynucleotide: (II) encodes the polypeptide of (S1), and contains a sequence with bases 254-520, or bases 1-2196 of a 2196 nucleotide sequence (S2), fully defined in the specification. Preferred Compound: The compound is particularly a polynucleotide of (S2), or an antisense of its fragment.

ACTIVITY - Neuroprotective; antimetabolite. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - (I) and (II) are used in diagnosis and treatment of neuropsychosis, and metabolic and developmental disturbances associated with uracil and thymine (claimed).

ADMINISTRATION - Administration is non-oral, particularly by injection. No dosage is suggested.

EXAMPLE - Cloning of **human** dihydropyrimidinase-related

protein-1 (**DRP-1**) 9.68 was performed by using **human** fetal RNA and then further studies were carried out.(34 pages)

L14 ANSWER 2 OF 23 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2003-05118 BIOTECHDS
TITLE: **Human** dihydropyrimidinase associated protein-1 (**DRP-1**) 8.8 and polynucleotides encoding it; vector-mediated recombinant protein gene transfer and expression in host cell for use in neuropsychosis and metabolic disorder therapy
AUTHOR: MAO Y; XIE Y
PATENT ASSIGNEE: BODE GENE DEV CO LTD SHANGHAI
PATENT INFO: CN 1361270 31 Jul 2002
APPLICATION INFO: CN 2000-135948 26 Dec 2000
PRIORITY INFO: CN 2000-135948 26 Dec 2000; CN 2000-135948 26 Dec 2000
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
OTHER SOURCE: WPI: 2002-751601 [82]
AB DERWENT ABSTRACT:
NOVELTY - **Human** dihydropyrimidinase associated protein-1 (**DRP-1**) 8.8, polynucleotides encoding it and DNA recombination process to produce the polypeptide, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: a method of applying the polypeptide in treating various diseases (e.g. neuropsychosis, uracil and thymine related metabolic disorder and development disorders), an antagonist against the polypeptide and its use in treatment, and the application of the polynucleotides encoding **human** dihydropyrimidinase associated protein-1 (**DRP-1**) 8.8.

L14 ANSWER 3 OF 23 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-15893 BIOTECHDS
TITLE: A **human** dihydropyrimidinase associated protein-1 (**DRP-1**) 9.35 polypeptide, and the polynucleotide encoding it, for treating e.g. nervous disease and development disorders; recombinant protein production and antagonist
AUTHOR: MAO Y; XIE Y
PATENT ASSIGNEE: BODE GENE DEV CO LTD SHANGHAI
PATENT INFO: CN 1331332 16 Jan 2002
APPLICATION INFO: CN 2000-116772 26 Jun 2000
PRIORITY INFO: CN 2000-116772 26 Jun 2000
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
OTHER SOURCE: WPI: 2002-340675 [38]
AB DERWENT ABSTRACT:
NOVELTY - A **human** dihydropyrimidinase associated protein-1 (**DRP-1**) 9.35 polypeptide (I), and the polynucleotide (II) encoding it, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) producing (I) recombinantly; and (2) an antagonist (III) of (I).
ACTIVITY - Tranquilizer; endocrine. No suitable data given.
MECHANISM OF ACTION - None given.
USE - (I) is useful for treating diseases e.g. nervous disease, development disorders. (III) is useful medically.
ADMINISTRATION - No details given.

L14 ANSWER 4 OF 23 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002243327 MEDLINE
DOCUMENT NUMBER: 21977651 PubMed ID: 11980920

TITLE: DAP kinase and **DRP-1** mediate membrane blebbing and the formation of autophagic vesicles during programmed cell death.
AUTHOR: Inbal Boaz; Bialik Shani; Sabanay Ilana; Shani Gidi; Kimchi Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: JOURNAL OF CELL BIOLOGY, (2002 Apr 29) 157 (3) 455-68. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020501
Last Updated on STN: 20030105
Entered Medline: 20020522

AB Death-associated protein kinase (DAPk) and DAPk-related protein kinase (**DRP**)-**1** proteins are Ca+2/calmodulin-regulated Ser/Thr death kinases whose precise roles in programmed cell death are still mostly unknown. In this study, we dissected the subcellular events in which these kinases are involved during cell death. Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of cell death, and extensive autophagy, which is typical of autophagic (type II) programmed cell death. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or **DRP-1** reduced membrane blebbing during the p55/tumor necrosis factor receptor 1-induced type I apoptosis but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of **DRP-1** or of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-gamma. Thus, both endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this kinase in the process of autophagy.

L14 ANSWER 5 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:265433 HCAPLUS
DOCUMENT NUMBER: 134:294084
TITLE: Differentially expressed genes associated with Her-2/neu overexpression
INVENTOR(S): Slamon, Dennis J.; Oh, Juliana J.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001025250	A1	20010412	WO 2000-US27649	20001006
W: AU, CA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1218394	A1	20020703	EP 2000-973424	20001006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				

PRIORITY APPLN. INFO.: US 1999-157923P P 19991006
WO 2000-US27649 W 20001006

AB The present invention provides **human** Her-2/neu overexpression modulated proteins (HOMPS) and polynucleotides encoding HOMPS polypeptides. The invention also provides HOMPS contg. expression vectors and host cells, HOMPS antibodies and methods of producing HOMPS. In addn., the invention provides methods for generating, identifying and manipulating HOMPS. The genes were identified by differential screening of gene expression in MCF7 cells in which the Her-2 was expressed at normal levels or overexpressed. Some of the cloned cDNAs were identified as coming from known genes or as splice variants from known genes. The patterns of regulation of these genes were similarly altered in ovarian and breast cancer cell lines that were similarly altered to show overexpression of her-2/neu.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 23 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001328399 MEDLINE
DOCUMENT NUMBER: 21276420 PubMed ID: 11279167
TITLE: rDrak1, a novel kinase related to apoptosis, is strongly expressed in active osteoclasts and induces apoptosis.
AUTHOR: Kojima H; Nemoto A; Uemura T; Honma R; Ogura M; Liu Y
CORPORATE SOURCE: Tissue Engineering Research Center (TERC), National Institute of Advanced Industrial Science and Technology (AIST), 1-1-1 Higashi, Tsukuba Ibaraki 305-8562, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 1) 276 (22) 19238-43.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB042195
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20030105
Entered Medline: 20010726

AB This is the first report of a novel serine/threonine kinase, rabbit death-associated protein (DAP) kinase-related apoptosis-inducing protein kinase 1 (rDRAK1), involved in osteoclast apoptosis. We searched for osteoclast-specific genes from a cDNA library of highly enriched rabbit osteoclasts cultured on ivory. One of the cloned genes has a high homology with **human** DRAK1 (hDRAK1), which belongs to the DAP kinase subfamily of serine/threonine kinases. By screening a rabbit osteoclast cDNA library and 5'-RACE (rapid amplification of cDNA ends), we obtained a full length of this cDNA, termed rDRAK1. The sequencing data indicated that rDRAK1 has 88.0, 44.6, 38.7, and 42.3% identity with hDRAK1, DAP kinase, **DRP-1**, and ZIP (zipper-interacting protein) kinase, respectively. To clarify the role of DRAK1 in osteoclasts, we examined the effect of three osteoclast survival factors (interleukin-1, macrophage colony-stimulating factor, and osteoclast differentiation-inducing factor) on rDRAK1 mRNA expression and the effect of rDRAK1 overexpression on osteoclast apoptosis. The results suggested that these three survival factors were proved to inhibit rDRAK1 expression in rabbit osteoclasts. After transfection of a rDRAK1 expression vector into cultured osteoclasts, overexpressed rDRAK1 was localized exclusively to the nuclei and induced apoptosis. Hence, rDRAK1 may play an important role in the core apoptosis program in osteoclast.

L14 ANSWER 7 OF 23 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001216755 MEDLINE

DOCUMENT NUMBER: 21153208 PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP-1** kinase by controlling dimerization and calmodulin binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP-1** is a pro-apoptotic Ca2+/calmodulin (CaM)-regulated serine/threonine kinase, recently isolated as a novel member of the DAP-kinase family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP-1** homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP-1** dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP-1**, and a target for efficient activation of the kinase by various apoptotic stimuli.

L14 ANSWER 8 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001240857 EMBASE
TITLE: Detection of drug-related problems in the community pharmacy: Registered users versus non-registered users.
AUTHOR: Barbero Gonzalez J.A.
CORPORATE SOURCE: Dr. J.A. Barbero Gonzalez, P Extremadura n 170, 28011 Madrid, Spain. a.barbero@wanadoo.es
SOURCE: Pharmaceutical Care Espana, (2001) 3/3 (204-215).
Refs: 21
ISSN: 1139-6202 CODEN: PCEACX
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The main goal of this study was to compare the kind and features of the drug-related problems (DRP) between patients with and without patient medication record in the pharmacy. 212 drug related problems were detected. 43,4% of these problems belongs to a drug related problem type 6, that is, adverse drug reaction (7,43% for patients without medication record and 18,78% for patients with the patient medication record). The physician was contacted in 44,3% of the total drug-related problems and accepted the 80,26% of the recommendations which the pharmacist made. The acceptance of the recommendations depended on the type of the drug-related

problem. So, the **DRP 1**, 2 and 6 were accepted nearly always. However, the type 3 (the drug is not effective in the patient) was not accepted in 38,5% occasions.

L14 ANSWER 9 OF 23 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2002043087 MEDLINE
DOCUMENT NUMBER: 21627562 PubMed ID: 11771764
TITLE: Aberrant expression of dihydropyrimidinase related proteins-2,-3 and -4 in fetal Down syndrome brain.
AUTHOR: Weitzdoerfer R; Fountoulakis M; Lubec G
CORPORATE SOURCE: Department of Pediatrics, University of Vienna, Austria.
SOURCE: JOURNAL OF NEURAL TRANSMISSION. SUPPLEMENTUM, (2001) (61) 95-107.
Journal code: 0425126. ISSN: 0303-6995.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020124
Last Updated on STN: 20020611
Entered Medline: 20020610

AB Pathfinding of growing axons to reach their target during brain development is a subtle process needed to build up contacts between neurons. Abnormalities in brain development in Down Syndrome (DS) are described in a couple of morphological reports but the molecular mechanisms underlying abnormal wiring in fetal DS brain are not yet elucidated. We therefore performed a study using the proteomic approach to show differences in protein levels involved in the guidance of axons between control and DS brain in early prenatal life. Proteins obtained from autopsy of **human** fetal abortus were applied on 2-dimensional gel, identified and quantified. We quantified 5 members of the semaphorin/collapsin family, the dihydropyrimidinase related proteins 1-4 and the collapsin response mediator protein-5 (CRMP-5) in 8 DS and 7 control cortex samples. **DRP-1** and CRMP-5 levels were comparable in the control and DS samples. Evaluation of DRP-2, DRP-3 and DRP-4 revealed significantly decreased levels of 2 of the 15 spots assigned to DRP-2 and increased levels of one spot assigned to DRP-3 and increased DRP-4 in DS brain. We conclude that as early as from the 19th week of gestation pathfinding cues of the outgrowing axons are impaired in DS. These findings may help to elucidate mechanisms leading to abnormalities in neural migration of DS brain.

L14 ANSWER 10 OF 23 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function

analysis of a novel death-associated protein (DAP) kinase-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to DAP kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP kinase **DRP-1**, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP kinase encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP kinase. Possible functional connections between DAP kinase and **DRP-1** are discussed.

L14 ANSWER 11 OF 23 MEDLINE

ACCESSION NUMBER:	2000284184 MEDLINE
DOCUMENT NUMBER:	20284184 PubMed ID: 10822341
TITLE:	Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium.
AUTHOR:	Johnston-Wilson N L; Sims C D; Hofmann J P; Anderson L; Shore A D; Torrey E F; Yolken R H
CORPORATE SOURCE:	Stanley Division of Developmental Neurovirology, Johns Hopkins University, Baltimore, MD 21287-4933, USA.. nlj@welchlink.welch.jhu.edu
SOURCE:	MOLECULAR PSYCHIATRY, (2000 Mar) 5 (2) 142-9. Journal code: 9607835. ISSN: 1359-4184.
PUB. COUNTRY:	ENGLAND: United Kingdom
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200008
ENTRY DATE:	Entered STN: 20000811 Last Updated on STN: 20000811 Entered Medline: 20000803

AB Severe psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder are brain diseases of unknown origin. No biological marker has been documented at the pathological, cellular, or molecular level, suggesting that a number of complex but subtle changes underlie these illnesses. We have used proteomic technology to survey postmortem tissue to identify changes linked to the various diseases. Proteomics uses two-dimensional gel electrophoresis and mass spectrometric sequencing of proteins to allow the comparison of subsets of expressed proteins among a large number of samples. This form of analysis was combined with a multivariate statistical model to study changes in protein levels in 89 frontal cortices obtained postmortem from individuals with

schizophrenia, bipolar disorder, major depressive disorder, and non-psychiatric controls. We identified eight protein species that display disease-specific alterations in level in the frontal cortex. Six show decreases compared with the non-psychiatric controls for one or more diseases. Four of these are forms of glial fibrillary acidic protein (GFAP), one is dihydropyrimidinase-related protein 2, and the sixth is ubiquinone cytochrome c reductase core protein 1. Two spots, carbonic anhydrase 1 and fructose biphosphate aldolase C, show increase in one or more diseases compared to controls. Proteomic analysis may identify novel pathogenic mechanisms of **human** neuropsychiatric diseases.

L14 ANSWER 12 OF 23 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000130832 MEDLINE
DOCUMENT NUMBER: 20130832 PubMed ID: 10664068
TITLE: Differential expression of dihydropyrimidinase-related protein genes in developing and adult enteric nervous system.
AUTHOR: Inagaki H; Kato Y; Hamajima N; Nonaka M; Sasaki M; Eimoto T
CORPORATE SOURCE: Department of Pathology, Nagoya City University Medical School, Mizuho-ku, Nagoya 467-8601, Japan.. hinagaki@med.nagoya-cu.ac.jp
SOURCE: HISTOCHEMISTRY AND CELL BIOLOGY, (2000 Jan) 113 (1) 37-41. Journal code: 9506663. ISSN: 0948-6143.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000407
Last Updated on STN: 20000407
Entered Medline: 20000324

AB Dihydropyrimidinase-related proteins (DRPs) are involved in axonal outgrowth and pathfinding. However, little is known about their significance in the enteric nervous system (ENS), the largest and most complex division of the peripheral nervous system. Using in situ hybridization (ISH) and northern blotting, we examined mRNA expression of **DRP-1**-4 transcripts in the developing and adult mouse digestive tract and in the adult **human** colon. ISH detected the mouse DRP-3 transcript in the developing ENS on embryonic day (E)12 and at the later stages as well as in the adult intestine. Mouse **DRP-1** and -2 transcripts appeared at E14. DRP-2 transcript was also detected in the adult intestine although **DRP-1** expression was lower in the adult. DRP-4 gene was not expressed in the ENS during development or adulthood whereas the signal was apparent in the developing and adult central nervous system (CNS). The DRP expression pattern in the **human** colon was similar to that of the mouse large intestine. Northern blot analysis showed that DRPs were differentially expressed in the mouse and **human** intestines, supporting the results of ISH. These data suggest that DRPs play a role not only in the CNS but also in the ENS.

L14 ANSWER 13 OF 23 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2000:124083 SCISEARCH
THE GENUINE ARTICLE: 282FD
TITLE: Differential expression of dihydropyrimidinase-related protein genes in developing and adult enteric nervous system
AUTHOR: Inagaki H (Reprint); Kato Y; Hamajima N; Nonaka M; Sasaki M; Eimoto T
CORPORATE SOURCE: NAGOYA CITY UNIV, SCH MED, DEPT PATHOL, MIZUHO KU, NAGOYA, AICHI 4678601, JAPAN (Reprint); NAGOYA CITY UNIV, SCH MED, DEPT BIOCHEM, MIZUHO KU, NAGOYA, AICHI 4678601, JAPAN;

NAGOYA CITY UNIV, SCH MED, DEPT PEDIAT, MIZUHO KU, NAGOYA, AICHI 4678601, JAPAN; UNIV TOKYO, GRAD SCH SCI, DEPT BIOL SCI, TOKYO 1130033, JAPAN
COUNTRY OF AUTHOR: JAPAN
SOURCE: HISTOCHEMISTRY AND CELL BIOLOGY, (JAN 2000) Vol. 113, No. 1, pp. 37-41.
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
ISSN: 0301-5564.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 18

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Dihydropyrimidinase-related proteins (DRPs) are involved in axonal outgrowth and pathfinding. However, little is known about their significance in the enteric nervous system (ENS), the largest and most complex division of the peripheral nervous system. Using in situ hybridization (ISH) and northern blotting, we examined mRNA expression of **DRP-1**-4 transcripts in the developing and adult mouse digestive tract and in the adult **human** colon. ISH detected the mouse DRP-3 transcript in the developing ENS on embryonic day (E)12 and at the later stages as well as in the adult intestine. Mouse **DRP-1** and -2 transcripts appeared at E14. DRP-2 transcript was also detected in the adult intestine although **DRP-1** expression was lower in the adult. DRP-4 gene was not expressed in the ENS during development or adulthood whereas the signal was apparent in the developing and adult central nervous system (CNS). The DRP expression pattern in the **human** colon was similar to that of the mouse large intestine. Northern blot analysis showed that DRPs were differentially expressed in the mouse and **human** intestines, supporting the results of ISH. These data suggest that DRPs play a role not only in the CNS but also in the ENS.

L14 ANSWER 14 OF 23 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of cell death-promoting DAP-kinase related protein kinase **DRP-1** and
INVENTOR(S): Kimchi, Adi
PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9944408	A1	20000105	AU 1999-44408		19990615
GB 2354522	A1	20010328	GB 2001-660		19990615
PRIORITY APPLN. INFO.:			US 1998-89294P	P	19980615
			WO 1999-US13411	W	19990615

AB A new protein kinase, DAP-Kinase related 1 protein (**DRP-1**), which is a novel homolog of DAP-kinase, has been isolated. and cDNA sequence and amino acid sequences of **human DRP-1** are reported. This novel calmodulin-dependent kinase is a cell death-promoting protein functioning in the biochem. pathway which involves DAP (death-assocd. protein)-kinase (e.g., forming a cascade of sequential kinases, one directly activating the other). Alternatively, the two kinases may operate to promote cell death in parallel pathways.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 23 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:725347 HCAPLUS

DOCUMENT NUMBER: 132:76851

TITLE: Identification of differentially expressed genes associated with HER-2/neu overexpression in **human** breast cancer cells

AUTHOR(S): Oh, Juliana J.; Grosshans, David R.; Wong, Steven G.; Slamon, Dennis J.

CORPORATE SOURCE: Department of Medicine, Division of Hematology and Oncology, UCLA School of Medicine, Los Angeles, CA, 90095-1678, USA

SOURCE: Nucleic Acids Research (1999), 27(20), 4008-4017
CODEN: NARHAD; ISSN: 0305-1048

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Amplification and resulting overexpression of the HER-2/neu proto-oncogene is found in .apprx.30% of **human** breast and 20% of **human** ovarian cancers. To better understand the mol. events assocd. with overexpression of this gene in **human** breast cancer cells, differential hybridization was used to identify genes whose expression levels are altered in cells overexpressing this receptor. Of 16,000 clones screened from an overexpression cell cDNA library, a total of 19 non-redundant clones were isolated including seven whose expression decreases (C clones) and 12 which increase (H clones) in assocn. with HER-2/neu overexpression. Of these, five C clones and 11 H clones have been confirmed to be differentially expressed by northern blot anal. This group includes nine genes of known function, three previously sequenced genes of relatively uncharacterized function and four novel genes without a match in GenBank. Examn. of the previously characterized genes indicates that they represent sequences known to be frequently assocd. with the malignant phenotype, suggesting that the subtraction cloning strategy used identified appropriate target genes. In addn., differential expression of 12 of 16 (75%) cDNAs identified in the breast cancer cell lines are also seen in HER-2/neu-overexpressing ovarian cancer cells, indicating that they represent generic assocns. with HER-2/neu overexpression. Finally, up-regulation of two of the identified cDNAs, one novel and one identified but-as-yet-uncharacterized gene, was confirmed in **human** breast cancer specimens in assocn. with HER-2/neu overexpression. Further characterization of these genes may yield insight into the fundamental biol. and pathogenetic effects of HER-2/neu overexpression in **human** breast and ovarian cancer cells.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 23 MEDLINE

ACCESSION NUMBER: 2000085748 MEDLINE
DOCUMENT NUMBER: 20085748 PubMed ID: 10619028
TITLE: C. elegans dynamin-related protein **DRP-1** controls severing of the mitochondrial outer membrane.
AUTHOR: Labrousse A M; Zappaterra M D; Rube D A; van der Bliek A M
CORPORATE SOURCE: Department of Biological Chemistry, University of California, Los Angeles School of Medicine 90095, USA.
CONTRACT NUMBER: GM51866 (NIGMS)
SOURCE: MOLECULAR CELL, (1999 Nov) 4 (5) 815-26.
Journal code: 9802571. ISSN: 1097-2765.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF166274
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000131
Last Updated on STN: 20000131
Entered Medline: 20000114

AB Little is known about the mechanism of mitochondrial division. We show here that mitochondria are disrupted by mutations in a C. elegans dynamin-related protein (**DRP-1**). Mutant **DRP-1** causes the mitochondrial matrix to retract into large blebs that are both surrounded and connected by tubules of outer membrane. This indicates that scission of the mitochondrial outer membrane is inhibited, while scission of the inner membrane still occurs. Overexpressed wild-type **DRP-1** causes mitochondria to become excessively fragmented, consistent with an active role in mitochondrial scission. **DRP-1** fused to GFP is observed in spots on mitochondria where scission eventually occurs. These data indicate that wild-type **DRP-1** contributes to the final stages of mitochondrial division by controlling scission of the mitochondrial outer membrane.

L14 ANSWER 17 OF 23 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000008691 MEDLINE
DOCUMENT NUMBER: 20008691 PubMed ID: 10543354
TITLE: Unhealthy eating behaviour in adolescents.
AUTHOR: Martin A R; Nieto J M; Jimenez M A; Ruiz J P; Vazquez M C; Fernandez Y C; Gomez M A; Fernandez C C
CORPORATE SOURCE: Escuela de Ciencias de la Salud, Area de Salud Publica, Universidad de Cadiz, Spain.. amelia.rodriguez@uca.es
SOURCE: EUROPEAN JOURNAL OF EPIDEMIOLOGY, (1999 Aug) 15 (7) 643-8.
Journal code: 8508062. ISSN: 0393-2990.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991123

AB In recent years, eating disorders (Anorexia and Bulimia Nervosa) have increased and are appearing at increasingly younger ages. They affect predominantly adolescent females 12 to 25 years of age. The objective of this study of adolescents is to detect and discuss unhealthy eating behaviour, defined by either of two factors: (1) following a slimming diet not advised or supervised by any person trained in health care; or (2) eating very large quantities at irregular times, not related to anxiety or stress. A transversal study has been undertaken of 630 school children of 14-18 years of age (average: 15.9 years) in Cadiz (Andalucia, Spain), using an anonymous self-reporting questionnaire to collect data on

personal and educational situation, on eating habits, on nutritive intake and knowledge of nutrition, and on dieting and physical exercise. The study has considered averages, ratios, statistical significance (chi2) and, as a measure of risk, the Disequality Ratio of Prevalence (DRP). Anomalous eating behaviour was detected in 46.3% (292), with females predominant by a ratio of 2:1. Comparing groups with anomalous and with normal eating habits, significant differences were detected in respect of: perception of body image ($p < 0.001$), frequency of weighing oneself ($p < 0.05$), periods of abstinence from eating (**DRP 1**.66; 95% confidence interval (CI): 1.66-2.37), provocation of vomiting (DRP 2.02; 95% CI: 1.13-3.65), use of laxatives (DRP 4.25: 95% CI: 1.08-9.63), and the exclusion of certain meals and types of food, mainly bread and cereals, fats and sugars. Conclusions are drawn on the substantial scale of unhealthy eating behaviour among adolescents in Cadiz. More adequate education on personal health and related social issues should be provided.

L14 ANSWER 18 OF 23 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000039612 MEDLINE
DOCUMENT NUMBER: 20039612 PubMed ID: 10574455
TITLE: Characterization of the **human** dihydropyrimidinase-related protein 2 (DRP-2) gene.
AUTHOR: Kitamura K; Takayama M; Hamajima N; Nakanishi M; Sasaki M; Endo Y; Takemoto T; Kimura H; Iwaki M; Nonaka M
CORPORATE SOURCE: Department of Biochemistry, Nagoya City University Medical School, Nagoya, Japan.
SOURCE: DNA RESEARCH, (1999 Oct 29) 6 (5) 291-7.
Journal code: 9423827. ISSN: 1340-2838.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB020764; GENBANK-AB020765; GENBANK-AB020766; GENBANK-AB020767; GENBANK-AB020768; GENBANK-AB020769; GENBANK-AB020770; GENBANK-AB020771; GENBANK-AB020772; GENBANK-AB020773; GENBANK-AB020774; GENBANK-AB020775; GENBANK-AB020776; GENBANK-AB020777; GENBANK-Z47338
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000131

AB The genes within the dihydropyrimidinase-related protein (DRP) family, were originally identified in **humans** by their homology to dihydropyrimidinase (DHP). Four members of this gene family, **DRP -1**, -2, -3 and -4, are expressed mainly in the fetal and neonatal brains of mammals and chickens, and have been implicated as intracellular signal transducers in the development of the nervous system. We isolated the **human** DRP-2 gene, and determined its transcriptional start site and exon/intron organization. The gene spanned more than 62 kb, and contained 14 exons with lengths ranging from 62 bp to 2606 bp. The transcriptional start site was determined by an RNase protection assay and 5' rapid amplification of cDNA ends (RACE), and a highly GC-rich promoter was identified that contained possible regulatory elements such as a TATA box, CAAT box and three GC boxes. Comparison of the phase and position of intron insertions within the **human** DRP-2 gene with those within **DRP-1**, DHP and two Caenorhabditis elegans DRP/DHP homologs, indicated that DRPs are more conserved in their exon/intron organization than DHP.

L14 ANSWER 19 OF 23 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 96278825 MEDLINE
DOCUMENT NUMBER: 96278825 PubMed ID: 8662830
TITLE: **Human** Ku autoantigen binds cisplatin-damaged DNA

but fails to stimulate **human** DNA-activated protein kinase.

AUTHOR: Turchi J J; Henkels K

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Wright State University School of Medicine, Dayton, Ohio 45435, USA.

CONTRACT NUMBER: CA64374 (NCI)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jun 7) 271 (23) 13861-7.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199608

ENTRY DATE: Entered STN: 19960911
Last Updated on STN: 20030218
Entered Medline: 19960826

AB We have identified a series of proteins based on an affinity for cisplatin-damaged DNA. One protein termed **DRP-1** has been purified to homogeneity and was isolated as two distinct complexes. The first complex is a heterodimer of 83- and 68-kDa subunits, while the second complex is a heterotrimer of 350-, 83-, and 68-kDa subunits in a 1:1:1 ratio. The 83- and 68-kDa subunits in each complex are identical. The 83-kDa subunit of **DRP-1** was identified as the p80 subunit of Ku autoantigen by N-terminal protein sequence analysis and reactivity with a monoclonal antibody directed against **human** Ku p80 subunit. The 68-kDa subunit of **DRP-1** cross-reacted with monoclonal antisera raised against the Ku autoantigen p70 subunit. The 350-kDa subunit was identified as DNA-PKcs, the catalytic subunit of the **human** DNA-activated protein kinase, DNA-PK. **DRP-1**/Ku DNA binding was assessed in mobility shift assays and competition binding assays using cisplatin-damaged DNA. Results indicate that DNA binding was essentially unaffected by cisplatin-DNA adducts in the presence or absence of DNA-PKcs. DNA-PK activity was only stimulated with undamaged DNA, despite the ability of Ku to bind to cisplatin-damaged DNA. The lack of DNA-PK stimulation by cisplatin-damaged DNA correlated with the extent of cisplatin-DNA adduct formation. These results demonstrate that Ku can bind cisplatin-damaged DNA but fails to activate DNA-PK. These results are discussed with respect to the repair of cisplatin-DNA adducts and the role of DNA-PK in coordinating DNA repair processes.

L14 ANSWER 20 OF 23 MEDLINE DUPLICATE 10

ACCESSION NUMBER: 97128821 MEDLINE

DOCUMENT NUMBER: 97128821 PubMed ID: 8973361

TITLE: A novel gene family defined by **human** dihydropyrimidinase and three related proteins with differential tissue distribution.

AUTHOR: Hamajima N; Matsuda K; Sakata S; Tamaki N; Sasaki M; Nonaka M

CORPORATE SOURCE: Department of Pediatrics, Nagoya City University Medical School, Japan.

SOURCE: GENE, (1996 Nov 21) 180 (1-2) 157-63.
Journal code: 7706761. ISSN: 0378-1119.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AB004669; GENBANK-AB004670; GENBANK-AB004671; GENBANK-AB004672; GENBANK-AB004673; GENBANK-AB004674; GENBANK-AB004675; GENBANK-AB004676; GENBANK-AB004677;

GENBANK-AB004678; GENBANK-AB006713; GENBANK-AB006714; GENBANK-AB006715; GENBANK-D78011; GENBANK-D78012; GENBANK-D78013; GENBANK-D78014

ENTRY MONTH: 199701

ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 20000303
Entered Medline: 19970122

AB We have isolated cDNA clones encoding dihydropyrimidinase (DHPase) from **human** liver and its three homologues from **human** fetal brain. The deduced amino acid (aa) sequence of **human** DHPase showed 90% identity with that of rat DHPase, and the three homologues showed 57-59% aa identity with **human** DHPase, and 74-77% aa identity with each other. We tentatively termed these homologues **human** DHPase related protein (**DRP**)-**1**, DRP-2 and DRP-3. **Human** DRP-2 showed 98% aa identity with chicken CRMP-62 (collapsin response mediator protein of relative molecular mass of 62 kDa) which is involved in neuronal growth cone collapse. **Human** DRP-3 showed 94-100% aa identity with two partial peptide sequences of rat TOAD-64 (turned on after division, 64 kDa) which is specifically expressed in postmitotic neurons. **Human** DHPase and DRPs showed a lower degree of aa sequence identity with Bacillus stearothermophilus hydantoinase (39-42%) and Caenorhabditis elegans unc-33 (32-34%). Thus we describe a novel gene family which displays differential tissue distribution: i.e., **human** DHPase, in liver and kidney; **human DRP-1**, in brain; **human** DRP-2, ubiquitously expressed except for liver; **human** DRP-3, mainly in heart and skeletal muscle.

L14 ANSWER 21 OF 23 MEDLINE DUPLICATE 11

ACCESSION NUMBER: 96067608 MEDLINE

DOCUMENT NUMBER: 96067608 PubMed ID: 7487948

TITLE: Identification of direct-repeat-binding protein 1 (**DRP-1**), a DNA-binding protein that binds specifically to the 'malic' enzyme gene promoter direct repeat element.

AUTHOR: Ford K G; Hornby D P; al Harrasy W S

CORPORATE SOURCE: Krebs Institute, Department of Molecular Biology and Biotechnology, University of Sheffield, U.K.

SOURCE: BIOCHEMICAL JOURNAL, (1995 Nov 1) 311 (Pt 3) 901-4.
Journal code: 2984726R. ISSN: 0264-6021.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199512

ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951221

AB The 'malic' enzyme (ME) gene promoter contains three main regulatory regions. One of these, the direct repeat element (DRE), contains tandem degenerate Sp1-binding sites separated by a 3 bp intervening sequence. We now show that a previously unreported 95 kDa protein, which we have designated **DRP-1**, binds strongly to the DRE region in a highly specific manner. Western-blot analysis confirms that this protein is not Sp1, which has been shown to bind to similar degenerate sites. Competitive binding assays using purified **DRP-1** further reveal that neither non-specific nor Sp1-consensus-site-containing oligonucleotides can displace those complexes formed between **DRP -1** and the DRE sequence, thus confirming sequence-specific binding by this protein. SDS/PAGE analysis of DRE-protein complexes isolated by direct excision and transplantation from retardation gels confirms the presence of the 95 kDa protein and, in addition, suggests

that more than one binding site exists for this protein within the DRE. This is in accord with the repeated nature of the DRE DNA sequence which contains two CACC box motifs.

L14 ANSWER 22 OF 23 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 12
ACCESSION NUMBER: 92262890 EMBASE
DOCUMENT NUMBER: 1992262890
TITLE: Acute effects of oral isosorbide dinitrate on exercise thallium-201 myocardial imaging in patients with stable angina pectoris. A randomized double-blind placebo-controlled clinical trial.
AUTHOR: Madias e. J.; Lee V.W.; Song S.S.
CORPORATE SOURCE: Cardiology Division, Mount Sinai City Hospital Center, 79-01 Broadway,Elmhurst, NY 11373, United States
SOURCE: American Journal of Noninvasive Cardiology, (1992) 6/4 (215-223).
ISSN: 0258-4425 CODEN: AJNCE4
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The acute effects of oral isosorbide dinitrate (ISDN) on myocardial perfusion was compared to placebo (PLC) using thallium-201 myocardial perfusion scintigraphy with bicycle ergometry in 31 patients with a history of stable angina pectoris and an exercise-induced thallium defect with resolution at rest, 31.7 .+-. 3.4 (SEM) days prior to an on-therapy stress test. Following a dose-finding trial, 15 patients were randomized to ISDN and 16 to PLC. The two patient groups were not significantly different at baseline. One hour following ISDN or PLC the patients underwent exercise thallium-201 stress testing. Exercise duration, total work load and peak double product were similar in the 2 groups of patients at both stress tests. Qualitative comparisons of the thallium images did not reveal any differences between the 2 groups. Also quantitative comparisons of thallium images did not reveal differences between the two groups in the regions of highest and lowest count rates per pixel, or percent defect rate of perfusion (DRP%) of the defect areas [**DRP % = 1** - (counts of the area with defect/counts of the area with highest count density)] during both tests. However, DRP% in the ISDN group following exercise was significantly lower after treatment (18.5 .+-. 3.1) than before (27.1 .+-. 2.3; $p < 0.001$), while the corresponding values for the PLC were not statistically different (25.2 .+-. 3.2 and 27.4 .+-. 1.4). Also although redistribution produced a statistically significant decrease in DRP% in comparison with the post-exercise images in the pretreatment and treatment phases of the PLC group and the pretreatment phase of ISDN group, the on-treatment DRP% change for the ISDN group was not statistically different (18.5 .+-. 3.1 vs. 12.4 .+-. 2.6). These results suggest that improvement in perfusion or more homogeneous distribution of coronary flow during exercise was effected by the oral administration of ISDN. However, this drug did not have a similar effect on the redistribution images. This reduction in the difference in count density between the areas with the highest counts and the ones identified as defects should be attributed to improvement in the rate of coronary blood flow to the originally poorly perfused regions, since the external work load and double product (reflecting myocardial oxygen demands) did not change between the 2 tests.

L14 ANSWER 23 OF 23 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 92059378 MEDLINE
DOCUMENT NUMBER: 92059378 PubMed ID: 1951635

TITLE: Xp21 dystrophin and 6q dystrophin-related protein. Comparative immunolocalization using multiple antibodies.
AUTHOR: Voit T; Haas K; Leger J O; Pons F; Leger J J
CORPORATE SOURCE: Department of Pediatrics, University of Dusseldorf, Federal Republic of Germany.
SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (1991 Nov) 139 (5) 969-76. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 20000303
Entered Medline: 19911217

AB A protein of Mr 400 K and slightly lower Mr than Xp21 dystrophin was detected in skeletal muscle from patients with Duchenne muscular dystrophy by three antibodies raised against the midrod and C-terminal portions of chicken dystrophin, and by antibodies to dystrophin-related protein. Immunocytochemistry showed continuous sarcolemmal staining of Duchenne muscle with these antibodies. Subcellular localization to the inner face of the plasma membrane of Duchenne muscle was demonstrated by immunoelectron microscopy using the model of a Duchenne patient deleted for most of the dystrophin gene. Other antibodies were specific for Xp21 dystrophin. In conclusion, a dystrophin homologue that may be identical to the previously described dystrophin-related protein (**DRP**) **1** is expressed in Duchenne muscle with intracellular distribution similar to Xp21 dystrophin in normal muscle.

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=> d his

     (FILE 'HOME' ENTERED AT 14:59:00 ON 20 MAY 2003)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 15:00:34 ON 20 MAY 2003
L1        115622 S CALMODULIN
L2         64490 S CALCIUM AND L1
L3         28975 S L2 (A) KINASE?
L4        232176 S CELL (A) DEATH
L5           109 S "DRP-1"
L6           478 S L3 AND L4
L7             9 S L5 AND L6
L8             5 DUP REM L7 (4 DUPLICATES REMOVED)
L9        387738 S APOPTOSIS
L10          578 S L3 AND L9
L11            9 S L5 AND L10
L12            6 DUP REM L11 (3 DUPLICATES REMOVED)
L13           55 S L5 AND HUMAN
L14           23 DUP REM L13 (32 DUPLICATES REMOVED)

=> s l4 or l9
L15      499589 L4 OR L9

=> s l14 and l15
L16            5 L14 AND L15

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17            5 DUP REM L16 (0 DUPLICATES REMOVED)

=> d 1-5 ibib ab
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L17 ANSWER 1 OF 5 MEDLINE
ACCESSION NUMBER: 2002243327 MEDLINE
DOCUMENT NUMBER: 21977651 PubMed ID: 11980920
TITLE: DAP kinase and **DRP-1** mediate membrane blebbing and the formation of autophagic vesicles during programmed **cell death**.
AUTHOR: Inbal Boaz; Bialik Shani; Sabanay Ilana; Shani Gidi; Kimchi Adi
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: JOURNAL OF CELL BIOLOGY, (2002 Apr 29) 157 (3) 455-68. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020501
Last Updated on STN: 20030105
Entered Medline: 20020522

AB Death-associated protein kinase (DAPk) and DAPk-related protein kinase (**DRP**)-**1** proteins are Ca+2/calmodulin-regulated Ser/Thr death kinases whose precise roles in programmed **cell death** are still mostly unknown. In this study, we dissected the subcellular events in which these kinases are involved during **cell death**. Expression of each of these DAPk subfamily members in their activated forms triggered two major cytoplasmic events: membrane blebbing, characteristic of several types of **cell death** , and extensive autophagy, which is typical of autophagic (type II) programmed **cell death**. These two different cellular outcomes were totally independent of caspase activity. It was also found that dominant negative mutants of DAPk or **DRP-1** reduced membrane blebbing during the p55/tumor necrosis factor receptor 1-induced type I **apoptosis** but did not prevent nuclear fragmentation. In addition, expression of the dominant negative mutant of **DRP-1** or of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino acid starvation, or administration of interferon-gamma. Thus, both endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this kinase in the process of autophagy.

L17 ANSWER 2 OF 5 MEDLINE
ACCESSION NUMBER: 2001328399 MEDLINE
DOCUMENT NUMBER: 21276420 PubMed ID: 11279167
TITLE: rDrak1, a novel kinase related to **apoptosis**, is strongly expressed in active osteoclasts and induces **apoptosis**.
AUTHOR: Kojima H; Nemoto A; Uemura T; Honma R; Ogura M; Liu Y
CORPORATE SOURCE: Tissue Engineering Research Center (TERC), National Institute of Advanced Industrial Science and Technology (AIST), 1-1-1 Higashi, Tsukuba Ibaraki 305-8562, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Jun 1) 276 (22) 19238-43. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB042195

ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20030105
Entered Medline: 20010726

AB This is the first report of a novel serine/threonine kinase, rabbit death-associated protein (DAP) kinase-related **apoptosis**-inducing protein kinase 1 (rDRAK1), involved in osteoclast **apoptosis**. We searched for osteoclast-specific genes from a cDNA library of highly enriched rabbit osteoclasts cultured on ivory. One of the cloned genes has a high homology with **human** DRAK1 (hDRAK1), which belongs to the DAP kinase subfamily of serine/threonine kinases. By screening a rabbit osteoclast cDNA library and 5'-RACE (rapid amplification of cDNA ends), we obtained a full length of this cDNA, termed rDRAK1. The sequencing data indicated that rDRAK1 has 88.0, 44.6, 38.7, and 42.3% identity with hDRAK1, DAP kinase, **DRP-1**, and ZIP (zipper-interacting protein) kinase, respectively. To clarify the role of DRAK1 in osteoclasts, we examined the effect of three osteoclast survival factors (interleukin-1, macrophage colony-stimulating factor, and osteoclast differentiation-inducing factor) on rDRAK1 mRNA expression and the effect of rDRAK1 overexpression on osteoclast **apoptosis**. The results suggested that these three survival factors were proved to inhibit rDRAK1 expression in rabbit osteoclasts. After transfection of a rDRAK1 expression vector into cultured osteoclasts, overexpressed rDRAK1 was localized exclusively to the nuclei and induced **apoptosis**. Hence, rDRAK1 may play an important role in the core **apoptosis** program in osteoclast.

L17 ANSWER 3 OF 5 MEDLINE
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: 21153208 PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP-1** kinase by controlling dimerization and calmodulin binding.
AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP-1** is a pro-apoptotic Ca2+/calmodulin (CaM)-regulated serine/threonine kinase, recently isolated as a novel member of the DAP-kinase family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP-1** homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP-1** dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain

and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP-1**, and a target for efficient activation of the kinase by various apoptotic stimuli.

L17 ANSWER 4 OF 5 MEDLINE
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in **apoptosis**.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; Kimchi A
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) kinase-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to DAP kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP kinase **DRP-1**, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced **apoptosis** in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in **apoptosis** and generated a "superkiller" mutant. A dominant negative fragment of DAP kinase encompassing the death domain was found to block **apoptosis** induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking **cell death** induced by DAP kinase. Possible functional connections between DAP kinase and **DRP-1** are discussed.

L17 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:811348 HCAPLUS
DOCUMENT NUMBER: 132:46958
TITLE: Cloning, sequence and therapeutic applications of **cell death**-promoting DAP-kinase related protein kinase **DRP-1** and
INVENTOR(S): Kimchi, Adi

PATENT ASSIGNEE(S): Yeda Research and Development Company Ltd., Israel; McInnis, Patricia A.
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9966030	A1	19991223	WO 1999-US13411	19990615
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9944408	A1	20000105	AU 1999-44408	19990615
GB 2354522	A1	20010328	GB 2001-660	19990615

PRIORITY APPLN. INFO.: US 1998-89294P P 19980615
WO 1999-US13411 W 19990615

AB A new protein kinase, DAP-Kinase related 1 protein (**DRP-1**), which is a novel homolog of DAP-kinase, has been isolated. and cDNA sequence and amino acid sequences of **human DRP-1** are reported. This novel calmodulin-dependent kinase is a **cell death**-promoting protein functioning in the biochem. pathway which involves DAP (death-assocd. protein)-kinase (e.g., forming a cascade of sequential kinases, one directly activating the other). Alternatively, the two kinases may operate to promote **cell death** in parallel pathways.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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E2            1     KIMCHE N/AU
E3          499 --> KIMCHI A/AU
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     (FILE 'HOME' ENTERED AT 14:59:00 ON 20 MAY 2003)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 15:00:34 ON 20 MAY 2003
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L2         64490 S CALCIUM AND L1
L3         28975 S L2 (A) KINASE?
L4        232176 S CELL (A) DEATH
L5           109 S "DRP-1"
L6           478 S L3 AND L4
L7             9 S L5 AND L6
L8             5 DUP REM L7 (4 DUPLICATES REMOVED)
L9        387738 S APOPTOSIS
L10          578 S L3 AND L9
L11            9 S L5 AND L10
L12            6 DUP REM L11 (3 DUPLICATES REMOVED)
L13           55 S L5 AND HUMAN
L14           23 DUP REM L13 (32 DUPLICATES REMOVED)
L15       499589 S L4 OR L9
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L18          499 S E3

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L20  ANSWER 1 OF 4  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER:   2002278596  EMBASE
TITLE:              DAP kinase and DRP-1 mediate membrane
                    blebbing and the formation of autophagic vesicles during
                    programmed cell death.
AUTHOR:             Inbal B.; Bialik S.; Sabanay I.; Shani G.; Kimchi
                    A.
CORPORATE SOURCE:   A. Kimchi, Dept. of Molecular Genetics, Weizmann Institute
                    of Science, Rehovot 76100, Israel.
                    Adi.kimchi@weizmann.ac.il
SOURCE:             Journal of Cell Biology, (29 Apr 2002) 157/3 (455-468).
                    Refs: 48
                    ISSN: 0021-9525  CODEN: JCLBA3
COUNTRY:            United States
DOCUMENT TYPE:      Journal; Article
FILE SEGMENT:       029     Clinical Biochemistry
LANGUAGE:           English
SUMMARY LANGUAGE:   English
AB   Death-associated protein kinase (DAPk) and DAPk-related protein kinase (
     DRP)-1 proteins are Ca(+2)/ calmodulin-regulated Ser/Thr
     death kinases whose precise roles in programmed cell death are still
     mostly unknown. In this study, we dissected the subcellular events in
     which these kinases are involved during cell death. Expression of each of
     these DAPk subfamily members in their activated forms triggered two major
     cytoplasmic events: membrane blebbing, characteristic of several types of
     cell death, and extensive autophagy, which is typical of autophagic (type
     II) programmed cell death. These two different cellular outcomes were
     totally independent of caspase activity. It was also found that dominant
     negative mutants of DAPk or DRP-1 reduced membrane
     blebbing during the p55/tumor necrosis factor receptor 1-induced type I
     apoptosis but did not prevent nuclear fragmentation. In addition,
     expression of the dominant negative mutant of DRP-1 or
     of DAPk antisense mRNA reduced autophagy induced by antiestrogens, amino
     acid starvation, or administration of interferon-.gamma.. Thus, both
```

endogenous DAPk and **DRP-1** possess rate-limiting functions in these two distinct cytoplasmic events. Finally, immunogold staining showed that **DRP-1** is localized inside the autophagic vesicles, suggesting a direct involvement of this kinase in the process of autophagy.

L20 ANSWER 2 OF 4 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 2002:977272 SCISEARCH
THE GENUINE ARTICLE: 620DD
TITLE: The DAP-kinase family of proteins: study of a novel group of calcium-regulated death-promoting kinases.
AUTHOR: Shohat G; Shani G; Eisenstein M; **Kimchi A (Reprint)**
CORPORATE SOURCE: Weizmann Inst Sci, Dept Mol Genet, IL-76100 Rehovot, Israel (Reprint); Weizmann Inst Sci, Dept Chem Serv, IL-76100 Rehovot, Israel
COUNTRY OF AUTHOR: Israel
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA-PROTEINS AND PROTEOMICS, (4 NOV 2002) Vol. 1600, No. 1-2, pp. 45-50.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 1570-9639.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 15

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB DAP-kinase (DAPk) is a Ca2+/calmodulin (CaM)-regulated Ser/Thr kinase that functions as a positive mediator of programmed cell death. It associates with actin microfilament and has a unique multidomain structure. One of the substrates of DAPk was identified as myosin light chain (MLC), the phosphorylation of which mediates membrane blebbing. Four additional kinases have been identified based on the high homology of their catalytic domain to that of DAPk. Yet, they differ in the structure of their extracatalytic domains and in their intracellular localization. One member of this family, **DRP-1**, also shares with DAPk both the property of activation by Ca2+/CaM and a specific phosphorylation-based regulatory mechanism. The latter involves an inhibitory type of autophosphorylation on a conserved serine at position 308, in the CaM regulatory domains of these two kinases. This phosphorylation, which occurs in growing cells, restrains the death-promoting effects of these kinases, and is specifically removed upon exposure of cells to various apoptotic stimuli. The dephosphorylation at this site increases the binding and sensitivity of each of these two kinases to their common activator-CaM. In DAR, the dephosphorylation of serine 308 also increases the Ca2+/CaM-independent substrate phosphorylation. In DPR-1, it also promotes the formation of homodimers necessary for its full activity. These results are consistent with a molecular model in which phosphorylation on serine 308 stabilizes a locked conformation of the CaM regulatory domain within the catalytic cleft and simultaneously also interferes with CaM binding. In **DRP-1**, it introduces an additional locking device by preventing homodimerization. We propose that this unique mechanism of autoinhibition, evolved to keep these death-promoting kinases silent in healthy cells and ensures their activation only in response to apoptotic signals. (C) 2002 Elsevier Science B.V. All rights reserved.

L20 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001216755 MEDLINE
DOCUMENT NUMBER: 21153208 PubMed ID: 11230133
TITLE: Autophosphorylation restrains the apoptotic activity of **DRP-1** kinase by controlling dimerization and calmodulin binding.

AUTHOR: Shani G; Henis-Korenblit S; Jona G; Gileadi O; Eisenstein M; Ziv T; Admon A; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: EMBO JOURNAL, (2001 Mar 1) 20 (5) 1099-113.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010425
Last Updated on STN: 20020420
Entered Medline: 20010419

AB **DRP-1** is a pro-apoptotic Ca2+/calmodulin (CaM)-regulated serine/threonine kinase, recently isolated as a novel member of the DAP-kinase family of proteins. It contains a short extra-catalytic tail required for homodimerization. Here we identify a novel regulatory mechanism that controls its pro-apoptotic functions. It comprises a single autophosphorylation event mapped to Ser308 within the CaM regulatory domain. A negative charge at this site reduces both the binding to CaM and the formation of **DRP-1** homodimers. Conversely, the dephosphorylation of Ser308, which takes place in response to activated Fas or tumour necrosis factor-alpha death receptors, increases the formation of **DRP-1** dimers, facilitates the binding to CaM and activates the pro-apoptotic effects of the protein. Thus, the process of enzyme activation is controlled by two unlocking steps that must work in concert, i.e. dephosphorylation, which probably weakens the electrostatic interactions between the CaM regulatory domain and the catalytic cleft, and homodimerization. This mechanism of negative autophosphorylation provides a safety barrier that restrains the killing effects of **DRP-1**, and a target for efficient activation of the kinase by various apoptotic stimuli.

L20 ANSWER 4 OF 4 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000094983 MEDLINE
DOCUMENT NUMBER: 20094983 PubMed ID: 10629061
TITLE: Death-associated protein kinase-related protein 1, a novel serine/threonine kinase involved in apoptosis.
AUTHOR: Inbal B; Shani G; Cohen O; Kissil J L; **Kimchi A**
CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2000 Feb) 20 (3) 1044-54.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20020420
Entered Medline: 20000214

AB In this study we describe the identification and structure-function analysis of a novel death-associated protein (DAP) kinase-related protein, **DRP-1**. **DRP-1** is a 42-kDa Ca(2+)/calmodulin (CaM)-regulated serine threonine kinase which shows high degree of homology to DAP kinase. The region of homology spans the catalytic domain and the CaM-regulatory region, whereas the remaining C-terminal part of the protein differs completely from DAP kinase and displays no homology to any known protein. The catalytic domain is also homologous to the recently identified ZIP kinase and to a lesser extent to the catalytic domains of DRAK1 and -2. Thus, DAP kinase **DRP-**

1, ZIP kinase, and DRAK1/2 together form a novel subfamily of serine/threonine kinases. **DRP-1** is localized to the cytoplasm, as shown by immunostaining and cellular fractionation assays. It binds to CaM, undergoes autophosphorylation, and phosphorylates an exogenous substrate, the myosin light chain, in a Ca(2+)/CaM-dependent manner. The truncated protein, deleted of the CaM-regulatory domain, was converted into a constitutively active kinase. Ectopically expressed **DRP-1** induced apoptosis in various types of cells. Cell killing by **DRP-1** was dependent on two features: the status of the catalytic activity, and the presence of the C-terminal 40 amino acids shown to be required for self-dimerization of the kinase. Interestingly, further deletion of the CaM-regulatory region could override the indispensable role of the C-terminal tail in apoptosis and generated a "superkiller" mutant. A dominant negative fragment of DAP kinase encompassing the death domain was found to block apoptosis induced by **DRP-1**. Conversely, a catalytically inactive mutant of **DRP-1**, which functioned in a dominant negative manner, was significantly less effective in blocking cell death induced by DAP kinase. Possible functional connections between DAP kinase and **DRP-1** are discussed.

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(FILE 'HOME' ENTERED AT 14:59:00 ON 20 MAY 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 15:00:34 ON 20 MAY 2003

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L2        64490 S CALCIUM AND L1
L3        28975 S L2 (A) KINASE?
L4       232176 S CELL (A) DEATH
L5          109 S "DRP-1"
L6          478 S L3 AND L4
L7            9 S L5 AND L6
L8            5 DUP REM L7 (4 DUPLICATES REMOVED)
L9       387738 S APOPTOSIS
L10         578 S L3 AND L9
L11           9 S L5 AND L10
L12           6 DUP REM L11 (3 DUPLICATES REMOVED)
L13          55 S L5 AND HUMAN
L14          23 DUP REM L13 (32 DUPLICATES REMOVED)
L15      499589 S L4 OR L9
L16           5 S L14 AND L15
L17           5 DUP REM L16 (0 DUPLICATES REMOVED)
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L18         499 S E3
L19          10 S L5 AND L18
L20           4 DUP REM L19 (6 DUPLICATES REMOVED)
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1	20030508	61	US 20030087411 A1	Death associated kinase containing ankyr in repeats (DAKAR) and methods of use
2	20030424	20	US 20030077624 A1	Collapsin response mediator protein-1

	Issue Date	Pages	Document ID	Title
1	20030501	78	US 20030082511 A1	Identification of modulatory molecules using inducible promoters
2	20030403	39	US 20030065157 A1	Genes expressed in lung cancer
3	20030320	196	US 20030054421 A1	Nucleic acids, proteins, and antibodies
4	20030306	31	US 20030044946 A1	Genes, mutations, and drugs that increase cellular resistance to damage and extend longevity in organisms from yeast to humans
5	20030306	202	US 20030044783 A1	Human genes and gene expression products
6	20030227	198	US 20030040617 A9	Nucleic acids, proteins and antibodies
7	20030227	41	US 20030040471 A1	Compositions isolated from skin cells and methods for their use
8	20030130	41	US 20030023990 A1	JNK3 MODULATORS AND METHODS OF USE
9	20030130	43	US 20030022835 A1	Compositions isolated from skin cells and methods for their use
10	20030116	63	US 20030013699 A1	Methods for treating alzheimer's disease and/or regulating levels of amyloid beta peptides in a subject

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11	20021121	30	US 20020173036 A1	Cell line and method of making and using same
12	20021024	753	US 20020155119 A1	Isolation and use of fetal urogenital sinus expressed sequences
13	20021010	15	US 20020147183 A1	Antiangiogenic agents
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15	20020725	28	US 20020098495 A1	Proteins associated with aging
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19	20020418	105	US 20020045253 A1	METHODS COMPRISING APOPTOSIS INHIBITORS FOR THE GENERATION OF TRANSGENIC PIGS
20	20020404	40	US 20020040010 A1	Use of agents to treat heart disorders
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25	20030422		US 6552177 B2	EH domain containing genes and proteins
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30	20030128		US 6511800 B1	Methods of treating nitric oxide and cytokine mediated disorders

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53	20010206		US 6184205 B1	GRB2 SH3 binding peptides and methods of isolating and using same
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58	19990824		US 5942389 A	Genes and genetic elements associated with sensitivity to cisplatin
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